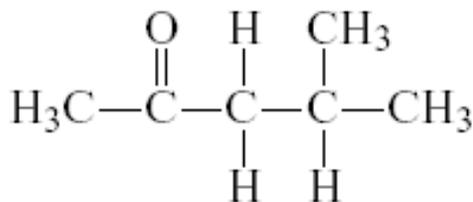




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Methyl Isobutyl Ketone



- Denaturant in rubbing alcohol, solvent for paints, industrial extraction processes and synthetic reactions
- Consumer uses include the cosmetic industry and dry cleaning preparations



Pre-chronic Studies

- ◆ Phillips, R. D., Moran, E., Dodd, D., Fowler, E., Kary, C., and O'Donoghue, J. (1987) A 14-week vapor inhalation study of methyl isobutyl ketone. *Fundam. Appl. Toxicol.* 9, 380–388

- ◆ **14-day studies**
 - Male and female F344/N rats and B6C3F₁ mice
 - Exposure via whole-body inhalation
 - MIBK exposure concentrations of 0, 100, 500, or 2,000 ppm 6 hours/day

- ◆ **14-week studies**
 - Male and female F344/N rats and B6C3F₁ mice
 - Exposure via whole-body inhalation
 - MIBK exposure concentrations of 0, 50, 250, or 1,000 ppm
 - 6 hours/day, 5 days per week

Relevant findings

◆ 14-day studies

- Increased liver weights in exposed male and female rats
- Increase kidney weights, tubular epithelium regeneration and hyaline droplet accumulation in males exposed to 500 and 2,000 ppm.

◆ 14-week studies

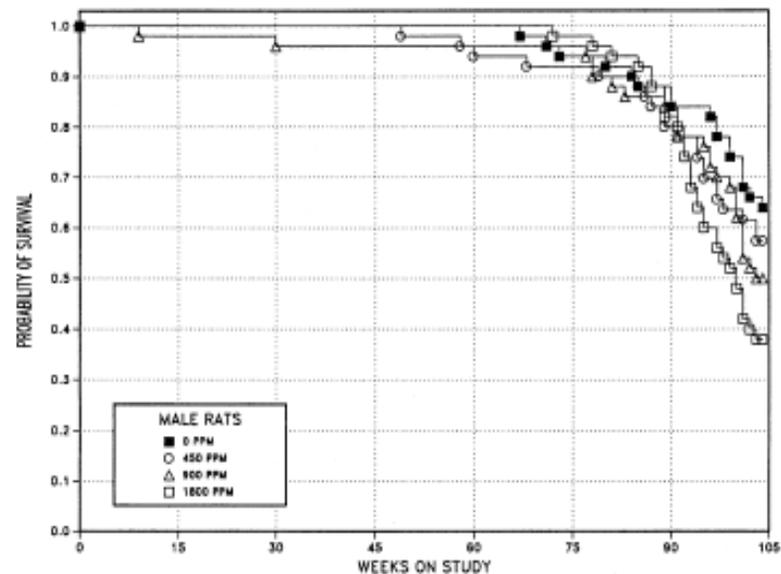
- Increased in the incidence and extent of hyaline droplet accumulation within the epithelial cells of proximal tubules in the kidneys of male rats exposed to 250 or 1,000 ppm MIBK.
- No other substantial pathologic changes or neurotoxic effects were reported.

Study Design

- ◆ **Whole-body Inhalation study**
- ◆ **Rats**
 - **Male and female F344/N rats**
 - **Dose groups-**
 - **Chamber Control, 450, 900, or 1,800 ppm**
- ◆ **Mice**
 - **Male and female B6C3F₁ mice**
 - **Dose groups-**
 - **Chamber Control, 450, 900, or 1,800 ppm**

Results: F344/N Rats

- ◆ Survival of males in the 1,800 ppm group was significantly less than that of the chamber controls.
- ◆ Survival of the 450 and 900 ppm males and all exposed group of females were similar to that of chamber controls



Effect of MIBK Exposure in Male Rats: Kidney lesions

Dose (ppm)	0	450	900	1,800
<u>Single Sections</u>				
Tubule Hyperplasia	1 (2.0)	11** (3.2)	3 (2.0)	18** (2.7)
Renal Tubule Adenoma	0	0	2	3
Renal Tubule Carcinoma	0	1	0	2
Adenoma or Carcinoma	0	0	2	4
<u>Step Sections</u>				
Tubule Hyperplasia	0	3 (2.0)	4 (2.0)	6* (2.3)
Renal Tubule Adenoma	2/50 (4%)	3/50 (6%)	1/50 (2%)	7/50 (14%)
Adenoma or Carcinoma	2	3	1	7
Poly-3 test	P=0.029	P=0.473	P=0.519N	P=0.062
<u>Combined</u>				
Tubule Hyperplasia	1 (2.0)	14* (2.9)	7* (2.0)	21** (2.5)
Renal Tubule Adenoma	2/50 (4%)	3/50 (6%)	3/50 (6%)	10/50 (20%)
Renal Tubule Carcinoma	0/50 (0%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adenoma or Carcinoma	2/50 (4%)	4/50 (8%)	3/50 (6%)	11/50 (22%)
Poly-3 test	P=<0.001	P=0.309	P=0.477	P=0.004

*P≤0.05

**P≤0.01

Effect of MIBK Exposure in Male and Female Rats: Kidney Toxicity

Dose (ppm)	0	450	900	1,800
Male				
Nephropathy	42 (2.0)	45 (2.6)	47 (2.4)	50* (3.1)
Papilla Mineralization	1 (1.0)	6* (1.2)	22**(1.6)	29**(1.5)
Pelvis Hyperplasia	1 (1.0)	5 (1.8)	6* (1.2)	19**(1.4)
Female				
Nephropathy	19 (1.4)	35**(1.5)	38**(1.5)	44**(1.9)

* $P \leq 0.05$

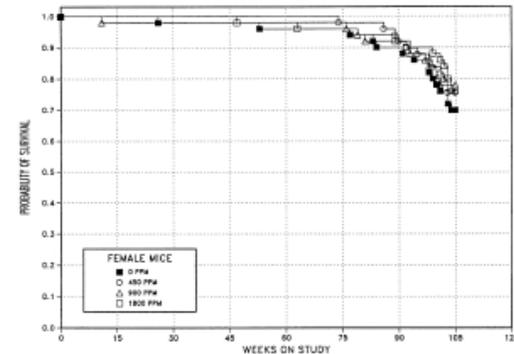
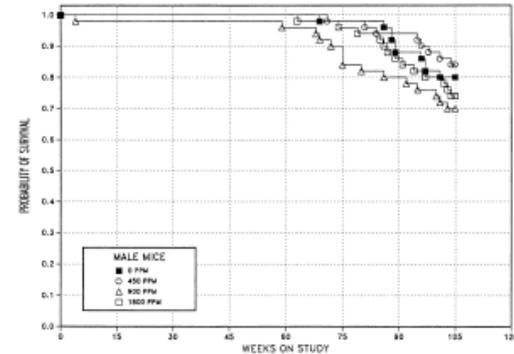
** $P \leq 0.01$

Additional Findings

- ◆ **Two female rats in the 1,800 ppm group developed renal mesenchymal tumors.**
- ◆ **Positive trends in the incidences of mononuclear leukemia in male rats that achieved statistical significance in the 1,800 ppm group and exceeded the historical range for chamber controls in inhalation studies.**

Results: B6C3F₁ Mice

- ◆ Survival of male and female mice was similar to that of the chamber controls.
- ◆ After week 17, body weights of 1,800 ppm females were less than those of the chamber controls.
- ◆ No clinical findings related to chemical exposure



Effect of MIBK Exposure in Mice: Liver

Dose (ppm)	0	450	900	1,800
Male				
Eosinophilic Focus	3	4	5	8
Hepatocellular Adenoma	17/50(34%)	25/50 (50%)	23/50 (46%)	34/50(68%)
Hepatocellular Carcinoma	12	12	10	9
Adenoma or Carcinoma	27/50(54%)	34/50 (68%)	28/50 (56%)	37/50 (74%)
Poly-3 test	P=0.028	P=0.146	P=0.368	P=0.019
Female				
Eosinophilic Focus	4	11*	10	14**
Hepatocellular Adenoma	13/50(26%)	15/50(30%)	20/50(40%)	23/50(46%)
Hepatocellular Carcinoma	6	5	6	11
Adenoma or Carcinoma	17/50(34%)	17/50(34%)	22/50(44%)	27/50(54%)
Poly-3 test	P=0.013	P=0.556N	P=0.228	P=0.035

N=50

*P_≤0.05

**P_≤0.01

Conclusions

- **Rats**
 - **Some evidence of carcinogenic activity in male rats based on increased incidences of renal tubule neoplasms.**
 - **Equivocal evidence of carcinogenic activity in female rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group.**
- **Mice**
 - **Some evidence of carcinogenic activity in male and female mice based on increased incidences of liver neoplasms.**

Conclusions

- ◆ **Increased incidences of mononuclear cell leukemia in 1,800 ppm male rats may have been related to methyl isobutyl ketone exposure.**
- ◆ **Exposure to methyl isobutyl ketone resulted in nonneoplastic lesions of the kidney suggestive of $\alpha_2\mu$ -globulin accumulation in male rats and nephropathy in female rats.**



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NTP Technical Reports Review Subcommittee Meeting

**Methyl Isobutyl Ketone
TR 538**

